SNF welcomes the opportunity to comment on the "No Significant Risk Level (NSRL) for the Proposition 65 Carcinogen ACRYLAMIDE", March 2005. SNF is the largest global and US manufacturer of acrylamide monomer. Our Product Stewardship Program involves, among other things, a toxicological evaluation program in several major medical centers in the US and abroad.

Based on a weight of evidence evaluation of experimental data, linear extrapolation is not relevant for acrylamide monomer. Our comments will focus on 4 major areas:

- Epidemiology data show that acrylamide may suppress tumor incidence not increase it as suggested in the NSRL.
- The weight of evidence shows that acrylamide reaction with DNA is not relevant to risk assessment.
- The genotoxicity of acrylamide is weak and not relevant to toxicological evaluation.
- Several of the rat tumors, especially the *tunica vaginalis* mesotheliomas, are not relevant to man.

We are including other comments along with reports that are in the process of being published.

1. Epidemiology of Pancreatic Cancer and Cancer of the Large Bowel

In the NSRL publication, considerable detail is allocated to the issue of whether acrylamide induces pancreatic tumors (See pages 10-14 and 26-27). The result of this discussion is that (pages 26-28) the upper bound human risk of pancreatic cancer from acrylamide is 2.8 $(mg/kg/day)^{-1}$. There was an SMR of 224 (a total of 9 tumors vs. 4.0 expected). Given an average acrylamide consumption of 1.0 μg/kg/day as cited by JECFA and using the CSF from the NSRL, the expected risk from acrylamide would be $3.6*10^{-4}$. Based on the US population of around 295,000,000, this equates to 106,200 deaths from pancreatic cancer. The American Cancer Society reports estimated deaths from pancreatic cancer (in the case of pancreatic cancer, this is interchangeable with

incidence) in 2004 as 31,270 per year (Jemal 2004). This becomes even more confusing as tobacco smoke is the only identified cause of this tumor.

Erdreich and Friedman (2004) discussed the observation that there was a single grouping (cell) which was positive for cancer of the pancreas. They pointed out that there was no biological plausibility to explain this phenomenon, nor was there a dose response or increase with duration of exposure. Selection of a single cell can be very complicated, as we will show below.

Focusing on cancer of the large bowel in the study would lead to a very different conclusion. The SMR for the cumulative exposure cell associated with cancer of the large bowel is 16, which represents a statistically significant decrease in incidence. That is, as a result of acrylamide exposure, cancer of the large bowel mortality was decreased by 84%. Unlike pancreatic cancer, there is a substantial difference between cancer incidence and mortality for cancer of the large bowel. Approximately 60% of affected individuals survive cancer of the large bowel. The American Cancer Society estimated that there were 106,370 deaths from cancer of the large bowel in 2004 (Jemal 2004). Using lifetime exposure estimates from Erdreich and Friedman (2004) for this cell (912 mg for Marsh vs. 843 mg from WHO), one might expect a substantial drop in large bowel cancer incidence and mortality (as high as 176,000 cases). Mucci *et al*. (2003) investigated cancer of the large bowel and saw a statistically significant trend ($p>0.01$) for a decrease of cancer of the large bowel and confirmed this finding. The magnitude of this decrease reached 40%. In case control studies conducted in Switzerland and Italy, an inverse trend ($p<0.05$) was reported for cancer of the large bowel while no other cancer type was changed in this study (Pelucchi 2003).

The question of biological plausibility of decreased large bowel cancer cannot be provided from rodent studies. There were no cancers of the large bowel in either of the rodent cancer studies (Friedman 1995; Johnson 1986). However, based on 3 epidemiology studies, one can draw the conclusion that acrylamide is protective against one of the most common human cancers and could be decreasing incidence of large bowel cancer by up to a 170,000 cases.

While the Marsh data may predict an upper bound lifetime increase of pancreatic cancer incidence of 126,000 cancer deaths, acrylamide apparently decreases large bowel cancer incidence by 11,900,000 cancers.

2. Use of the Linearized Model

OEHHA has chosen to use a low-dose linear approach for the dose response because "a genotoxic mechanism is likely" and because "evidence (for a non-genotoxic mechanism) is fairly limited". In the report, the evidence in support of a genotoxic mechanism for tumor induction is limited. Clearly there is substantial evidence that acrylamide is genotoxic, an issue we will discuss later, but the relationship between this activity at very high doses in mice and tumorigenicity in rats remains to be established. We are enclosing a table that summarizes the weight of the evidence for genotoxic and non-genotoxic mechanisms. The use of the linearized model for acrylamide is inappropriate and technically inaccurate justify on the basis of the scientific literature (CIR 2003; Streffer 2004; Bolt 2003)

Weight of the Evidence for Using/Not Using a Stochastic Model for Acrylamide Risk Assessment	
In favor of a genotoxic (stochastic) carcinogen model	**Against a genotoxic carcinogen model (*i.e.*, in favor of a threshold)**
Acrylamide is genotoxic. It is positive in dominant lethal test, spot test, heritable translocation, etc.	Acrylamide is genotoxic through chromosomal effects and not gene mutations. Acrylamide is not active in tests for gene mutations, even under conditions where enzymatic formation of glycidamide is favored.
The acrylamide metabolite, glycidamide, binds to DNA. Glycidamide binds to the 7 position in guanine and, to a much lesser extent, the 3 position in adenine	The glycidamide adducts are not in the base pairing region. The regions bound by glycidamide are on the wrong side of the DNA molecule to influence base pairing.
	The mutagenicity is very weak. Allen *et al.* showed that there would be no significant mutagenic response at the doses which are carcinogenic.
	The mode of genotoxicity is known. Sickles *et al.* have shown that acrylamide binds to *krp* proteins at very low doses (<0.1mM). These proteins are responsible for chromosomal segregation. Since acrylamide acts on proteins there will be a no effect level. This is born out by the data.
	Cell transformation is independent of glycidamide formation. Park *et al.* showed that if the conversion of acrylamide to glycidamide is blocked, there is no effect on the rate of cell transformation. (In the same studies, acrylonitrile induced cell transformation was significantly inhibited).
	Acrylamide breaks thyroid cell DNA under conditions where no glycidamide adducts are observed. When acrylamide treated thyroid cells in culture are

	There is no specificity associated with induction of DNA adducts. This does not explain the organ specificity and necessitates another significant pathway. Acrylamide induces cell proliferation in target organs, which explains specificity. Induction of cell proliferation is a non-stochastic event. This is a critical event to the tumorigenic process
	Mouse skin tumor data, which have been reported, are not relevant to man. Mouse skin tumors are produced via a mechanism which is not relevant to humans. Shipp *et al.* have concluded that initiation of mouse skin tumors involves the *ras* oncogene. This oncogene is not involved with human cancer.
	A Pathology Working Group has concluded that in the case of *Tunica vaginalis* mesotheliomas, based on morphology and distribution, these tumors are not produced by a genotoxic mechanism. The report of this PWG is attached. This is in agreement with the observations of Damjanov. This conclusion was based on the following: a. the location of the tumors; b. the tumors only appeared at the end of the study; c. there were no tumors in the females; d. the morphology was unremarkable (same as background).

3. Acrylamide is a clastogen with very weak genotoxicity

Acrylamide is negative in *in vitro* tests for gene mutation (Bolt 2003, Bolt 2004). These include the Ames test, mouse lymphoma and CHO HGPRT assays. Allen *et al*. (Allen 2005a) have pointed out that the acrylamide is an extremely weak genotoxin and that the genotoxicity does not contribute to the carcinogenicity. Using categorical regression to estimate potency as a point of departure and a linear extrapolation to zero, they concluded that mutagenicity was too weak to be involved with carcinogenicity. Bolt *et al*. (Bolt 2003; Bolt 2004; Streffer 2004) classified acrylamide as a clastogen, recognizing that acrylamide did not induce gene mutations. They pointed out that clastogens, in contrast chemicals which cause gene mutations, demonstrate a practical threshold. Wall, McConnell *et al*., as part of a pathology working group, reread the slides from the Johnson study and also concluded that acrylamide was not a genotoxic carcinogen. DNA adducts do not explain the organ specificity (Wall 2005). Lafferty *et al*. (Lafferty 2005; Lafferty 2004)) showed that at tumorigenic doses, acrylamide induced cell proliferation in thyroid and *tunica vaginalis* but not liver. The data are clear that a non-genotoxic action is the primary driving force for tumor formation and the genotoxicity is a secondary contributor at best. The correct analysis is that acrylamide is a carcinogen and a genotoxin.

The mechanism of genotoxicity has been established (Sickles 1992; Sickles 2004). Acrylamide inhibits *krp* enzyme activity and thereby alters chromosomal segregation. Acrylamide inhibits *krp*2 and *krp*1a. This is similar to many other carcinogens (Bolt 2003). These carcinogens are considered to be non-stochastic (Bolt 2004). A copy of the Sickles 2004 report is included as an addendum to these comments.

4. Testicular mesotheliomas are not relevant to man which significantly changes the calculated risk.

OEHHA has chosen to include *tunica vaginalis* mesotheliomas in their risk assessment. Damjanov and Friedman (1998) and (Shipp 1999b) have published that these tumors are not relevant to man. There is a substantial endocrinological difference between the male

Fischer 344 rat and man wherein this strain of rat is particularly and uniquely dependent upon circulating prolactin. In order to definitively establish the relevance of these tumors to human health risk assessment, we convened a Pathology Working Group (PWG). We are including a copy the report of this PWG for your consideration. Below are the conclusions of the Pathology Group:

- The Fischer 344 rat is not a good model for testicular effects.
- The TVMs in this study were rat specific and more likely F344 specific and not relevant to other species including man.
- A genotoxic mechanism is not likely involved as:
    - the liver was not a target and no non-scrotal areas of the mesothelium were involved;
    - the tumors had a late onset;
    - the tumors were present in only one sex (males);
    - there was no evidence of early onset (noted only after 92 weeks).
- Hormonal profile, particularly as relates to prolactin, of the Fischer 344 rat is not relevant to man.
- Hormonal imbalance is the most likely mechanism of tumor formation. Since the hormone profile is not relevant to man, this mechanism is not relevant to man.
- Testicular neoplasms are extremely rare in man and more common in the rat.
- Tumor morphology was not unique but the same as control tumors.

These tumors should be excluded from the risk assessment.

5. Acrylamide Does Not Compromise Cellular Genomes

Classification of acrylamide as a genotoxic carcinogen would be based on a chemical reaction of acrylamide with the cellular genome which induces changes in the decoding of that genome. Changes in DNA decoding under these circumstance are not directed but rather are random (Maniere 2005). As a consequence, miscoding of many proteins would

be anticipated due to the changes in the linear sequence of the DNA. This miscoding is a lethal event. Mutagens such as *N*-dimethylnitrosamine, acetylaminofluorene and dimethylaminoazobenzene induce cellular lethality in their target organs. In contrast acrylamide does not kill cells but rather stimulates them (Lafferty 2004; Lin 2000). This is most clear *in vitro* in the stimulation of microtubule synthesis by acrylamide (Lin 2000). There is no necrosis in the target tissues (Burek 1980)

6. More Specific Comments

Mammary fibroadenomas are not relevant to risk assessment

The same metabolic anomaly in prolactin metabolism that causes consideration of mammary fibroadenomas to be in question is relevant to mammary gland of female rats. We have previously provided reports documenting differences in aging of the female Fischer 344 rat wherein these animals go through a pseudo pregnancy, which is progesterone mediated, rather than what occurs in humans (menopause) which is estrogen mediated (Shipp 1999a). We also provided literature documenting that there is no malignant counterpart for this tumor. The data are clear that this tumor is an anomaly of the rat, especially the Fischer 344 rat.

Failure to Site Allen *et al*

Earlier we pointed out that genotoxicity did not account for acrylamide oncogenicity. We showed that the nature of the clastogenic lesion suggested that it was not active at low doses. We also demonstrated that morphological analysis by a PWG concluded that genotoxicity was not the operative lesion. This is clearest in a publication by Allen *et al* (Allen 2005b) which was not sited in the NSRL. Allen showed that when a dose response analysis was performed on acrylamide mutagenicity, there was no biological activity at the oncogenic doses.

Failure to Site Lafferty *et al.*

There are many publications which demonstrate the mode of action of acrylamide. These deal with receptor interactions and hormone levels. However, Lafferty *et al* showed that

cell proliferation could be detected at the oncogenic dose (Lafferty 2004). This accounts for the organ specificity for acrylamide. This continues to underscore the minimal contribution of genotoxicity to acrylamide oncogenicity. In this study he showed at 2.0 mg/kg/day there was cell proliferation in thyroid and *tunica vaginalis* but not liver.

7. Line by line comments:

Page ii, Para 2, Line 4. Delete "central nervous system" as the incidence of these tumors was not significantly increased in male rats in either the Johnson or Friedman study.

Page 1, para 2, line 1. The first sentence is misleading. It should read: "Acrylamide, most likely through its epoxide metabolite, glycidamide, is genotoxic."

Page 1, para 2, last sentence. Based on the lag in development of P-450 in humans, one would not expect children to be more sensitive but rather less sensitive. This sentence should be deleted as it raises concerns which do not exist.

Page 2, para 4, line 6. The term "rat testes" should be changed to "*tunica vaginalis*". There was no increased incidence of testicular tumors.

Page 3, para 2. The discussion of acrylamide carcinogenicity in mice should be attenuated, as administration of TPA was required for tumorigenic activity. Acrylamide alone was devoid of activity.

Page 4, para 2. The discussion of the FDA audit is complicated as there is no direct record of the audit findings. The audit has been lost or never reported formally.

Page 6, Table 2, Mammary Gland. The line combining all tumors is incorrect. Fibromas should not be combined with adenomas and adenocarcinomas as they represent a different embryological tissue of origin, have different pathological progressions, and are under different hormonal regulation from mammary tissue. These should be separated out.

Page 6, Table 2, Central Nervous System. This combines all CNS sites and all glial cell types. It is no longer the practice to combine these tumor sites and cell sites. These should be reported separately and by location (*e.g.*, spinal cord, brain and as astrocytic, oligodendrytic, etc.). It produces a substantial change in the statistics when done properly.

Page 8, Table 4, Mammary gland. The same comment about splitting out the fibromas from the adenomas and adenocarcinomas applies.

Page 8, Table 4, Central Nervous System. The same comment about splitting out the locations and cell types applies here.

Page 9 Table 5, Central Nervous System. The same comment about splitting out the locations and cell types applies here.

Page 9, last para. As sited earlier, a PWG report by EPL on the relevance of *tunica vaginalis* mesotheliomas should be included. Particularly their relevance to man.

Page 10, end of section. While a conclusion of the significance of the tumors is relevant, a discussion on the relevance of these tumors to man should be included. These tumors are progesterone generated while human cancer is estrogen generated. This is discussed in the Crump references.

Page 10, last para, line 1. Marsh did not detect a "significant association between cumulative exposure and risk" but rather "statistically significant mortality at the highest cumulative exposure".

Page 12, last para. The NSRL documentation has 3 pages on the issue of the questionable increase in pancreatic cancer but nothing on the substantial and significant decrease in large bowel cancer discussed earlier. We strongly believe that this discussion of human data should include the three independent studies, each of which conclude that there is a statistically significant decrease in large bowel cancer. It is remarkable that three different methodologies on three different populations gave the same results.

Page 14, para 3, line 3. The words "that a genotoxic mechanism is likely" imply that there is some weight of evidence that genotoxic modes have more support. The reality is that genotoxicity is taken as the default unless it can be disproved (proving a negative is extremely difficult). The word "likely" should be changed to "assumed". The Table, which we presented earlier, supports this notion.

Page 14 last, para Line 2. The words "unpublished industry reports" are misleading. These reports were prepared by a private contractor with industry financial support. To our knowledge, they are the only comprehensive, tumor-by-tumor analysis of acrylamide oncogenicity. In a peer review by TERA, a committee chaired by Bette Meeke of Health Canada concluded that the only way to determine the role of genotoxicity or other modes of action was to prepare a tumor-by-tumor analysis.

Page 15, line 2. "In all cases, a genotoxic mode…reports". The genotoxicity cannot account for the organ specificity of acrylamide as the adducts are formed uniformly in all organs. Furthermore, the genotoxicity is clastogenic in nature rather than producing gene mutations which makes the explanation even more tenuous. Finally, Allen *et al.* (2005) point out that acrylamide is a weak mutagen and cannot qualitatively account for the carcinogenicity. While OEHHA reserves the right to agree with WHO, it is not scientifically sound to make the statement in this paragraph.

Page 15, para 2, line 3. The discussion of site concordance is not clear. Reference to the sites of murine tumors is not appropriate. In the case of these murine tumors, co-administration of TPA was necessary. It is not reasonable to expect humans to be treated with large doses of TPA. It is more scientifically sound to discuss rat tissue versus human tissue. If acrylamide is carcinogenic in man it almost necessarily must be a different site as the mechanisms operative in rats are not relevant to man and the *tunica vaginalis* mesotheliomas and fibromas are not relevant to man. Lack of site concordance is an out of date toxicological notion based on aromatic amine toxicology. With the exception of aromatic amines in rats (but not dogs or mice), virtually all of the OSHA human carcinogens have site concordance. One of Koch's hypotheses is that the experimental

agent must induce the lesion. Parenthetically, it was only after site concordance was demonstrated in dogs that the carcinogenicity of aromatic amines was verified.

Page 15, para 6, line 4. Comparative mutagenic potency between acrylamide and ethylene oxide is not relevant to the discussion of cancer potency. This is especially true when Allen points out that acrylamide is a weak mutagen. It is much less potent than heterocyclic amines (Durling 2005). This paragraph should be deleted.

Page 16, para 2, line 11. "Maniere *et al.* …" may not be relevant. We find positive comet assays in tissues which are incapable of metabolizing acrylamide. These tissues have no glycidamide DNA adducts while they have positive comet for double strand breaks in DNA. The micronucleus data sited before this reference is reflective of clastogenic events and not necessarily DNA breaks.

Page 16, para 2, line 18. The statement that "additional research to identify … could improve risk assessment" is not consistent with your current presentation. The data cited above that double strand breaks occur in thyroids without DNA adduct formation is in press. We are providing a copy of the Pathology Working Group report by EPL to dismiss the *tunica vaginalis* mesotheliomas. We have supported the Allen study and the work by Lafferty *et al.* These are not seriously considered in your conclusions. Furthermore, calling 10, 20 and 50 mg/kg "low doses" is not correct. Should liver tumors be found in mice and not rats, these become part of the issue of the relevance of mouse liver tumors, which is highly questionable. This whole discussion of dose is academic because in humans the adduct ratio of AM-VAL to GLY-VAL is the same in the high dose of 3 mg/kg as in the background. To complete the discussion in this paragraph, OEHHA should point out that the adduction does not occur in the base-pairing region of DNA and put the significance of these lesions into context.

Page 16, para 3. Again, the discussion of EO is not relevant. A comprehensive literature review of causative agents in rats and mice coupled with their biological relevance to man would make more sense. As Crump *et al*. pointed out, there are several agents which produce *tunica vaginalis* mesotheliomas in Fischer rats but not other strains of rats. This

argues, as does the EPL report, that these tumors are Fischer rat specific and not relevant to man. Parenthetically, oral administration of EO only produces fore-stomach tumors.

Page 17, para 1, line 6. Martenson's observations did not occur "under cellular conditions" as his assays were conducted at room temperature and in the presence of an excess of tubules. Sickles repeated his observations but when he conducted the assay at 37°C, rather than at room temperature, he saw an effect. In addition, as the concentration of tubules decreased, the effect was accentuated. This is the most sensitive property of acrylamide: inhibition of kinesin occurs at a lower concentration than any other observable effect (0.5 μM).

Page 17, para 3. The discussion of prolactin is disjointed. Regulatory control of prolactin levels in males and females is quite different. Comparing the results of Ali *et al.* (1983) in males with Khan *et al.* (1999) in females is not appropriate and should be split out into separate paragraphs. In the case of females, Crump *et al.* speculate that the effect is manifested on pseudo-pregnancy which cannot be assayed in the young rats studied by Khan *et al*. In order to test the Crump hypothesis, older animals must be used.

Page 18, para 4, line 3. Fennel *et al*. (2005) have published on the rate of dermal absorption of acrylamide in humans. This absorption is slow and incomplete.

Page 22. para 5, line 1. While it is true that there are reasons to "suspect that early life exposures to acrylamide may result in greater tumor induction", there are also reasons to suspect that the opposite is true. As cited earlier, an argument can be made that due to the lack of development of CYP2E1 early in life, exposure would not represent a greater risk. It might be useful to balance this paragraph with the PB/PK considerations.

Page 23, para 2, line 2. The phorbol ester issue is academic as it is unlikely that individuals will be exposed to TPA. In addition the pathway involved in this response is not active in humans. This paragraph should be deleted.

Page 23, para 3. This paragraph is correct and does not need the misleading information presented earlier.

Page 23, para 4. "adults at the initiation of the study". 5-6 week old rats are not adults. They are not sexually mature and are still growing.

Page 25, para 1. "No adjustment factors". There are not many materials where the metabolic profile has been studied around the world. There is striking consistency in the responses. No adjustment factor is needed for intra-species variability.

Page 26, Section HUMAN DATA. This section is enormously misleading and completely inconsistent with American Cancer Society statistics on the incidence of pancreatic cancer. It is also unclear how OEHHA intends to handle the strikingly reproducible and prominent inhibition of large bowel cancer, clearly a much more significant phenomenon. This must be discussed, however.

Conclusion

Based on the review by the EPL PWG, we believe that the *tunica vaginalis* mesotheliomas should not be considered. Similarly, benign mammary fibroadenomas, which have no malignant counterpart, should also not be considered. The risk assessment should be based on thyroid tumors. In Table 10, the cancer potency estimates for the thyroid range from 0.24 to 0.44 mg/kg/day with a geometric mean of 0.32 mg/kg/day. The resulting NSRL will be 2.2 µg/day. However, using Benchmark Dose methodology with a BMD 0.21 mg/kg/day for the thyroid tumors and a margin of safety of 300 (based on the substantial human data and mode of action), the NSRL should be 47 µg/day.

References

Allen, B., Zeiger, E., Lawrence, G., Friedman, M., and Shipp, A. (2005b). Dose-response modeling of *in vivo* genotoxicity data for use in risk assessment: Some approaches illustrated by an analysis of acrylamide. *Regul Toxicol Pharmacol* 41, 6-27.

Bolt, H.M. (2003). Genotoxicity - threshold or not? Introduction of cases of industrial chemicals. *Toxicol Lett* 140-141, 43-51.

Bolt, H.M., and Degen, G. H. (2004). Human Carcinogenic Risk Evaluation, Part II: Contributions of the EUROTOX Specialty Section for Carcinogenesis. *Toxicol Sci* 81, 3-6.

Durling, L.J., and Abramsson-Zetterberg, L. (2005). A comparison of genotoxicity between three common heterocyclic amines and acrylamide. *Mutat Res* 580, 103-10.

Fennell, T.R., Sumner, S.C., Snyder, R.W., Burgess, J., Spicer, R., Bridson, W.E., and Friedman, M.A. (2005). Metabolism and hemoglobin adduct formation of acrylamide in humans. *Toxicol Sci* 85, 447-59.

Friedman, M.A., Dulak, L., and Stedham, M.A. (1995). A lifetime oncogenicity study in rats with acrylamide. *Fundamental and Applied Toxicology* 25, 95-105.

Jemal, A., Tiwari, R.C., Murray, T., Ghafoor, A., Samuels, A., Ward, E., Feuer, E.J., and Thun, M.J. (2004). Cancer Statistics, 2004. *CA Cancer J Clin* 54, 8-29.

Johnson, K.A., Gorzinski, S.J., Bodner, K.M., Campbell, R.A., Wolf, C.H., Friedman, M.A., and Mast, R.W. (1986). Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. *Toxicol Appl Pharmacol* 85, 154-68.

Lafferty, J.S., Kamendulis, L.M., Kaster, J., Jiang, J., and Klaunig, J.E. (2004). Subchronic acrylamide treatment induces a tissue-specific increase in DNA synthesis in the rat. *Toxicol Lett* 154, 95-103.

Lin, W.W., Friedman, M.A., Wang, X.F., and Abou-Donia, M.B. (2000). Acrylamide-regulated neurofilament expression in rat pheochromocytoma cells. *Brain Res* 852, 297-304.

Maniere, I., Godard, T., Doerge, D.R., Churchwell, M.I., Guffroy, M., Laurentie, M., and Poul, J.M. (2005). DNA damage and DNA adduct formation in rat tissues following oral administration of acrylamide. *Mutat Res* 580, 119-29.

Pelucchi, C., Franceschi, S., Levi, F., Trichopoulos, D., Bosetti, C., Negri, E., and La Vecchia, C. (2003). Fried potatoes and human cancer. *Int J Cancer* 105, 558-60.

Shipp, A., and Lawrence, G. (1999a). The Biological Role of Acrylamide-Induced Benign Fibroadenomas in the Aging Female F344 Rats to Human Health Outcomes, p. 46. ICF Consulting, The K.S. Crump Group, Inc., 602 East Georgia, Ruston, Louisiana 71270, Ruston, LA.

Shipp, A., and Lawrence, G. (1999b). Consideration of the Potency Classification of Acrylamide Based on the Incidence of Tunica Vaginalis Mespotheliomas (TVMs) in Male Fischer 344 Rats, p. 47. The K.S.Crump Group, Inc., 602 East Georgia, Ruston, Louisiana 71270, Reston, LA.

Sickles, D. (1992). Toxic Neurofilamentous Axonopathies and Fast Anterograde Axonal Transport. IV. In Vitro Analysis of Transport Folowing Acrylamide and 2,5-Hexanedione. *Toxicology Letters* 61, 199-204.

Sickles, D.W. (2004). Kinesin and Kinesin Related Proteins: Common Sites of Acrylamide Toxicity. Medical College of Georgia, Augusta, GA.

Streffer, C., Bolt, H.M., Follesdal, D., Hengstler, J.G., Jacob, P., Oughton, D., Priess, K., Rehbinder, E., and Swaton, E. (2004). *Environmental Standards - Dose-Effect Relations in the Low Dose Range and Risk Evaluation*. Springer-Verlag., Berlin.

Wall, H., McConnell, E., *et al*. (2005). Pathology Working Group Analysis of Tunica Vaginalis Mesotheliomas Induced by Acrylamide. Pathology Associates, Inc. (PAI), Research Triangle Park, NC.